Stereocontrolled Synthesis of the Tetracyclic Core Framework of (–)-Lemonomycin

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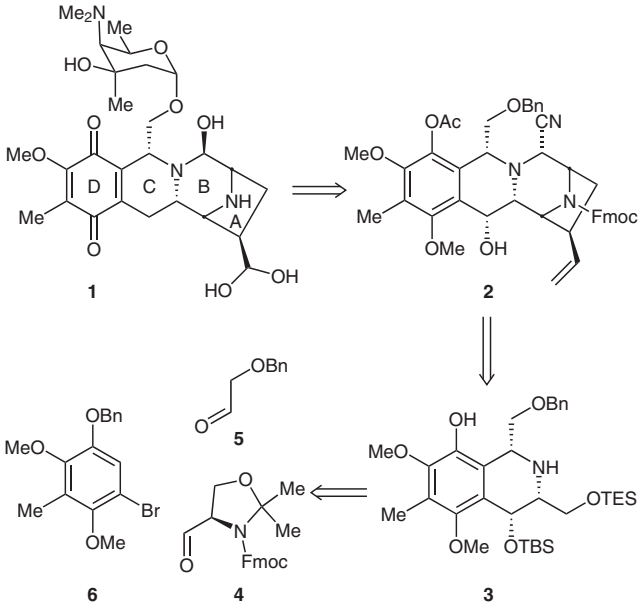
Abstract: In a convergent approach, an advanced intermediate (**2**) in a projected total synthesis of the alkaloid (–)-lemonomycin (**1**) was prepared from readily available starting materials. The key transformations were a Pictet–Spengler cyclization, a Strecker-type amino alkylation, and an *N*-acyliminium cyclization.

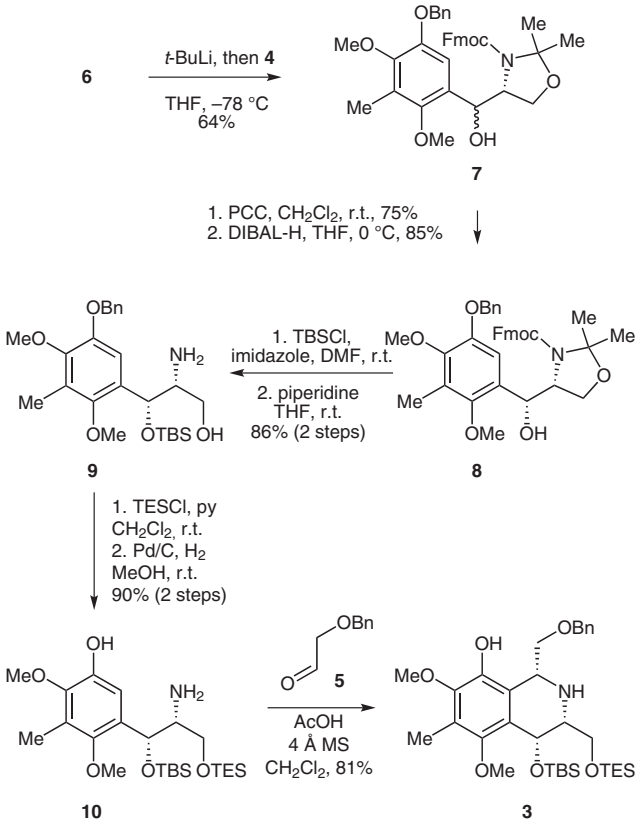
Key words: lemonomycin, antitumor antibiotic, tetrahydroisoquinoline, acyliminium cyclization, Pictet–Spengler reaction

(–)-Lemonomycin (**1**), a tetrahydroisoquinoline antitumor antibiotic,[1] was first isolated from a fermentation broth of *Streptomyces candidus* (LL-AP191) in 1964.[2] The compound was found to exhibit potent antibiotic activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecium*, for example, as well as high cytotoxic properties against a human colon cancer cell line (HCT-116). Despite its early isolation, the structure of this complex alkaloid could not be elucidated before 2000, when this goal was finally achieved by He and co-workers.[3] Lemonomycin (**1**) exhibits rare structural features such as a unique 2,6-dideoxy-4-amino sugar attached to a complex bridged tetracyclic core, a surprisingly stable hydrate functionality and an unstable hemiaminal moiety (Scheme 1).



Scheme 1 Structure and retrosynthetic analysis of **1**

No wonder that **1** has attracted the attention of the synthetic community for quite a while, and indeed, several approaches to lemonomycin derivatives and intermediates have been reported.[4] However, only one total synthesis of the natural product was completed thus far by Stoltz et al. in 2003.[5] Our retrosynthetic analysis of **1** leads back to key intermediate **2**, which contains the entire core fragment of the molecule. Removal of the benzylic hydroxy function, attachment of the amino sugar and elaboration of the hydrate functionality, as well as the labile quinone and hemiaminal moieties should be carried out at a late stage of the synthesis. Herein, we report a stereocontrolled access to enantiomerically enriched tetracycle **2** via tetrahydroisoquinoline **3**, which in turn is assembled from readily available starting materials **4**,[6] **5**, and **6**.[7] As illustrated in Scheme 2, the synthesis of **3** was started by con-



Scheme 2 Synthesis of tetrahydroisoquinoline **3**

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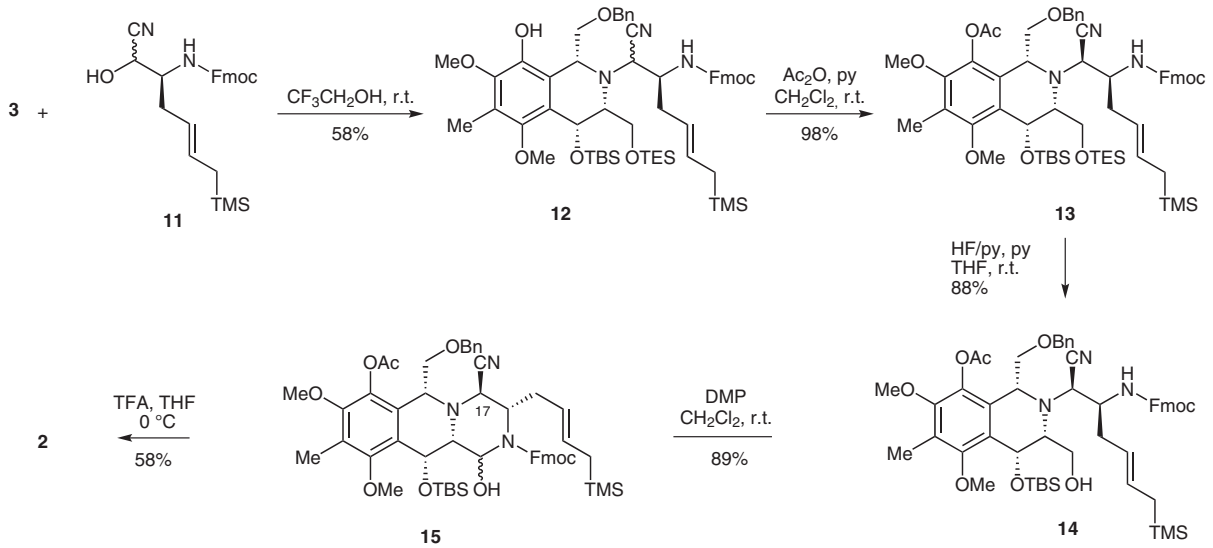
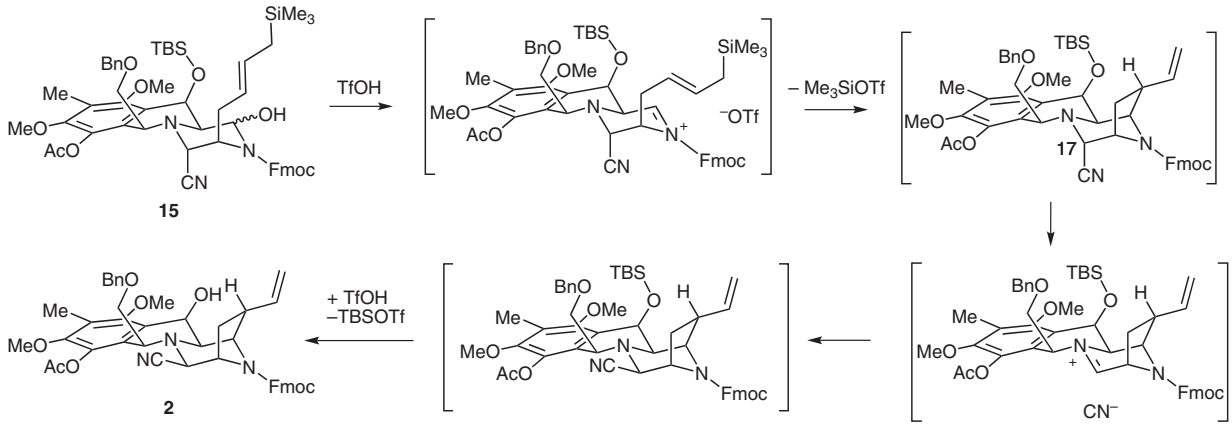
verting bromide **6** into the organolithium derivative, which was added to aldehyde **4** to afford secondary alcohol **7** as a 2.5:1 mixture of the *syn* and *anti* diastereomers. This mixture was subjected to an oxidation–reduction sequence in order to obtain the *syn* diastereomer **8** as the only product. *O*-TBS protection followed by simultaneous removal of the Fmoc and acetonide protecting groups smoothly provided amino alcohol **9**. Protection of the primary hydroxy function as triethylsilyl ether and deprotection of the phenol OH group[8] furnished intermediate **10** as a suitable substrate for the Pictet–Spengler reaction.[9] In fact, tetrahydroisoquinoline **3** was generated as a single diastereomer via slow addition of benzyloxy acetaldehyde **5** to a mixture of **10**, acetic acid and molecular sieves.[10] Addition of cyanohydrin sidechain **11**[11] in trifluoroethanol furnished amino nitrile **12** as the main diastereomer in acceptable yield (Scheme 3). Acetylation of the free phenol OH function provided acetate **13**.[12] To set the stage for the closure of the piperazine ring, the primary OTES function was deprotected with HF in pyridine to give alcohol **14**. Dess–Martin periodinane oxidation[13] led to the aldehyde which was attacked in situ by the Fmoc-protected nitrogen to furnish tricyclic hemiaminal **15**. Treatment of **15** with trifluoroacetic acid in THF triggered a cascade reaction (Scheme 4) by generating an acyliminium cation, which due to the steric repulsion from the neighboring OTBS group, was intercepted by the *si* face of the allylsilane moiety. Thus, the vinyl sidechain was directed into the desired *S* configuration. Subsequently, the cyano group at C-17 was isomerized into the less hindered equatorial position via an iminium ion intermediate and the TBS group was removed (Scheme 4). The resulting tetracycle **2** contains all stereocenters with correct relative[14] and absolute configurations as required for the synthesis of the (–)-lemonomycin aglycon.

In summary, we have developed a concise thirteen-step synthesis of the tetracyclic lemonomycin core fragment **2**[15] from simple building blocks with complete control over all six stereocenters. Conversion of **2** to (–)-lemonomycin (**1**) is currently under investigation in our laboratories.



Scheme 3 Synthesis of tetracyclic key intermediate **2**



Scheme 4 Cascade sequence from **15** to **2**

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Acknowledgment

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References and Notes

(1) For a recent review of tetrahydroisoquinoline alkaloids, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 16–69.
(2) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83.
(3) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067.
(4) (a) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476. (b) Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. *Chem. Commun.* **2005**, 394. (c) Couturier, C.; Schlama, T.; Zhu, J. *Synlett* **2006**, 1691. (d) Vincent, G.; Chen, Y.; Lane, J. W.; Williams, R. M. *Heterocycles* **2007**, *72*, 385.
(5) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000.
(6) Rush, J.; Bertozzi, C. R. *Org. Lett.* **2006**, *8*, 131.
(7) Preparation of aryl bromide **6** was performed via a five-step sequence from 2,6-dimethoxytoluene according to a method developed recently by us.
(8) No cyclization product was obtained performing the Pictet–Spengler reaction with the corresponding benzyl-protected phenol.
(9) For a recent review of the Pictet–Spengler reaction, see: Youn, S. W. *Org. Prep. Proc. Int.* **2006**, *38*, 505.
(10) Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796.
(11) (a) The (*E*)-(5-bromopent-2-enyl)trimethylsilane side chain employed in the enantioselective Myers' alkylation reaction was prepared by cross-metathesis between allyl-TMS and allyl bromide. (b) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401. (c) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322.
(12) Using the unprotected phenol in this reaction sequence led to the undesired formation of the quinone system upon treatment with Dess–Martin periodinane.
(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(14) The atom connectivities of all key intermediates were proven by through-bond correlation NMR techniques. In particular the structure of the rigid tetracyclic core in compound **2** was in full agreement with the NOEs and all ^{1}H–^{1}H coupling constants.
(15) **Synthesis of Tetrahydroisoquinoline 3**: Acetic acid (5 μL, 0.078 mmol) and powdered 4 Å molecular sieves were sequentially added to a solution of amino phenol **10** (75 mg, 0.16 mmol) in CH_2Cl_2 (2 mL). The resulting solution was degassed by three freeze-pump-thaw cycles. A solution of benzyloxy acetaldehyde **5** (25 μL, 0.171 mmol, 95%) in CH_2Cl_2 (1 mL) was slowly added via a syringe pump to the degassed solution over a period of 8.5 h. After stirring for 20 h at r.t., including the time of the addition, the reaction suspension was filtered through Whatman No. 5 filter paper to remove the molecular sieves. Sat. aq $NaHCO_3$ solution (40 mL) was added to the filtrate and the resulting biphasic solution was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH, 99:1, then 98:2, then 9:1) to afford tetrahydroisoquinoline **3** as pale yellow foam (77 mg, 81% after recovery of the unreacted starting material); R_f 0.51 (CH_2Cl_2–MeOH, 20:1); $[\alpha]_D^{20}$ +57.5 (*c* = 2.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 5 H), 5.08 (d, *J* = 2.2 Hz, 1 H), 4.60 (dd, *J* = 12.2, 13.2 Hz, 2 H), 4.42 (t, *J* = 5.9 Hz, 1 H), 3.85 (dd, *J* = 3.8, 5.4 Hz, 2 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.61 (d, *J* = 4.3 Hz, 1 H), 3.24 (m, 2 H), 2.26 (s, 3 H), 0.92 (t, *J* = 7.9 Hz, 6 H), 0.88 (s, 9 H), 0.56 (dd, *J* = 4.2, 7.9 Hz, 9 H), 0.20 (s, 3 H), 0.00 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 145.8, 142.5, 138.0, 128.3, 127.7, 127.6, 125.1, 122.5, 121.4, 73.9, 73.1, 63.7, 61.8, 61.3, 60.5, 59.4, 49.3, 25.9, 18.0, 9.7, 6.7, 4.3, 4.3, –4.5, –5.1. HRMS (180 °C, 70 eV): *m/z* calcd for $C_{33}H_{56}O_6NSi_2$: 618.3634; found: 618.3624.
Synthesis of 12: Tetrahydroisoquinoline **3** (78 mg, 0.127 mmol) and cyanohydrin **11** (55 mg, 0.127 mmol) were dissolved in anhyd 2,2,2-trifluoroethanol (800 μL). The reaction mixture was allowed to stir at r.t. for 24 h. The solvent was evaporated and the crude residue was purified by flash column chromatography (hexanes–EtOAc, 7:1) to afford a 1.6:1 mixture of two diastereomers of **12** (29 mg, 23% less polar diastereomer, 46 mg, 35% more polar diastereomer; 75 mg, 58%, combined yield). R_f 0.69, 0.66 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ +34.8 (*c* = 0.65, CHCl3). ^{1}H NMR (400 MHz, $CDCl_3$; major diastereomer): δ = 7.77 (m, 2 H), 7.61 (m, 2 H), 7.41 (m, 2 H), 7.27–7.34 (m, 5 H + 2 H), 6.07 (m, 1 H), 5.43–5.59 (m, 1 H), 5.35 (m, 1 H), 5.20 (m, 1 H), 4.49–4.61 (m, 2 H), 4.30–4.46 (m, 2 H + 1 H), 4.24 (m, 1 H + 1 H), 4.08 (m, 1 H), 3.97 (m, 1 H), 3.81 (m, 3 H), 3.71 (m, 1 H), 3.70 (m, 3 H), 3.42 (m, 1 H), 2.93 (t, *J* = 10.6 Hz, 1 H), 2.55 (m, 1 H), 2.24 (s, 3 H), 2.21 (m, 1 H), 1.65 (m, 1 H), 1.37 (m, 1 H), 0.92 (m, 9 H), 0.85 (s, 9 H), 0.60 (m, 6 H), 0.18 (s, 3 H), –0.02 (m, 9 H), –0.08 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, two sets of signals corresponding to two rotamers, * denotes the minor rotamer): δ = 157.7*, 155.6, 150.0, 146.1, 146.1*, 144.2*, 144.1, 143.9, 143.8*, 141.7, 141.6*, 141.3*, 141.2, 138.0, 137.9*, 131.7, 130.6, 128.4, 128.4*, 128.8*, 128.8, 127.7*, 127.7, 127.6*, 127.6, 127.0, 127.0*, 125.3, 125.2*, 123.6, 123.1, 123.1*, 122.1, 121.2*, 121.1, 120.7, 120.5*, 120.0*, 119.9, 76.9, 73.1, 73.1*, 67.1, 63.4*, 62.9, 62.1*, 61.6*, 61.4, 60.7, 60.3*, 60.1, 57.6, 57.2*, 53.2, 53.1*, 50.0*, 49.6, 47.2, 34.0, 26.0, 25.7*, 23.1, 18.7*, 18.0, 9.7, 6.8, 4.3, –1.9, –2.0, –4.9, –5.1. HRMS (100 °C, 70 eV): *m/z* calcd for $C_{58}H_{83}O_8N_3Si_3Na$: 1056.5386; found: 1056.5402.
Synthesis of 13: Acetic anhydride (13 μL, 0.134 mmol) and pyridine (18 μL, 0.223 mmol) were sequentially added to a solution of phenol **12** (46 mg, 0.045 mmol) in CH_2Cl_2 (0.7 mL) at r.t. After stirring for 16 h, sat. aq $NaHCO_3$ solution (20 mL) was added and the resulting solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexanes–EtOAc, 5:1) to furnish acetate **13** (47 g, 98%) as single product. R_f 0.69 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ –136 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.6 Hz, 2 H), 7.60 (dd, *J* = 3.1, 4.3 Hz, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.28–7.35 (m, 2 H + 5 H), 5.42–5.59 (m, 1 H), 5.38 (m, 1 H), 5.02–5.25 (m, 1 H), 4.58 (m, 1 H), 4.27–4.47 (m, 5 H), 4.24 (m, 1 H), 4.09 (m, 1 H), 3.95 (m, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.44 (m, 1 H + 1 H), 2.88 (m, 1 H), 2.49 (m, 1 H), 2.27 (s, 3 H), 2.23 (s, 3 H), 2.21 (m, 1 H), 1.60 (m, 1 H), 1.37 (m, 2 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 0.87 (s, 9 H), 0.60 (dd, *J* = 7.9, 7.9 Hz, 6 H), 0.20 (s, 3 H), –0.01 (s, 3 H), –0.02 (s, 3 H), –0.03 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$, two sets of signals, * denotes the minor rotamer): δ = 168.4, 168.4*, 155.6, 154.9, 150.8, 144.1*, 143.9, 141.3, 138.3, 138.1*, 136.7, 136.6*, 131.5, 130.5*, 128.3, 128.3*, 127.9, 127.8, 127.6, 127.0, 127.0*, 125.2, 125.2*, 124.6, 124.6*, 124.1, 124.0*, 122.3, 119.9, 77.6, 72.8, 67.0, 62.9, 62.5*, 61.3, 60.6, 60.4, 57.5, 57.0*,

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53.8, 53.6*, 50.3*, 49.8, 47.2, 34.0, 26.0, 23.1, 20.5, 20.4*, 18.8*, 18.0, 9.9, 6.8, 4.3, –1.8, –2.0, –4.8, –4.9. HRMS (120 °C, 70 eV): *m/z* calcd for $C_{60}H_{85}O_9N_3Si_3Na$: 1098.5491; found: 1098.5505.

Synthesis of 14: Compound **13** (86 mg, 0.080 mmol) was dissolved in a mixture of 30% HF–pyridine, (100 μL), pyridine (400 μL) and anhyd THF (2.7 mL). The reaction mixture was stirred at r.t. for 30 min. After total consumption of the starting material the reaction was quenched with buffer solution (pH 7.00, 20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexanes–EtOAc, 3:1) to furnish primary alcohol **14** (68 mg, 88%) as single product. R_f 0.43 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ +31.8 (*c* = 0.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.59 (m, 2 H), 7.40 (m, 2 H), 7.28–7.35 (m, 7 H), 5.49 (m, 1 H), 5.22 (m, 1 H), 5.16 (m, 1 H), 4.55 (m, 2 H), 4.32–4.43 (m, 4 H), 4.24 (t, *J* = 6.8 Hz, 1 H), 4.00 (m, 1 H), 3.94 (m, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.55 (m, 1 H), 3.46 (m, 1 H), 3.11 (m, 1 H), 2.48 (m, 1 H), 2.27 (s, 3 H), 2.23 (m, 1 H + 3 H), 1.35 (m, 2 H), 0.86 (m, 9 H), 0.20 (s, 3 H), –0.02 (s, 3 H), –0.03 (s, 6 H), –0.05 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 156.0, 154.6, 150.9, 143.9, 141.3, 138.3, 136.8, 131.9, 128.4, 127.9, 127.7, 127.4, 127.1, 125.2, 124.7, 124.5, 122.1, 120.2, 119.9, 77.8, 72.9, 67.1, 63.9, 61.7, 61.3, 61.0, 60.6, 58.0, 54.2, 49.4, 47.1, 34.1, 25.9, 23.1, 20.4, 18.0, 9.9, –1.8, –2.0, –4.8, –5.0. HRMS (150 °C, 70 eV): *m/z* calcd for $C_{54}H_{71}O_9N_3Si_2Na$: 984.4627; found: 984.4600.

Synthesis of 15: Primary alcohol **14** (53 mg, 0.055 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C, then Dess–Martin periodinane (67 mg, 0.22 mmol) was added. After stirring at 0 °C for 2 h the cooling bath was removed and the reaction mixture was stirred at r.t. for another 30 min. Sat. $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ solution (10 mL) were added and the mixture was extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexanes–EtOAc, 5:1) to furnish an epimeric mixture of the two diastereomeric carbinolamines **15** (47 mg, 89%). R_f 0.71 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ +6.5 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (m, 2 H), 7.56 (m, 2 H), 7.28–7.44 (m, 9 H), 5.59 (m, 1 H), 5.37 (m, 1 H), 5.15 (m, 1 H), 4.86–5.05 (m, 1 H), 4.79 (m, 1 H), 4.67 (m, 1 H), 4.35–4.61 (m, 6 H), 4.30, 4.22 (m, 1 H), 3.66–3.76 (m, 6 H), 3.43 (m, 1 H), 3.13 (m, 1 H), 2.38–2.60 (m, 2 H), 2.36, 2.32 (s, 3 H), 2.22 (m, 3 H), 1.60 (m, 2 H), 0.82, 0.79 (s, 9 H), 0.18 (m, 3 H), –0.03 (s, 3 H), –0.06 (s, 6 H), –0.09 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.8, 157.3, 157.0, 152.4, 145.6, 145.5, 143.3, 143.3, 140.3, 138.3, 133.0, 129.9, 129.8, 129.4, 129.3, 129.2, 129.2, 129.1, 127.4, 127.1, 126.9, 126.8, 124.8, 123.3, 122.1, 122.0, 118.8, 75.4, 75.3, 73.1, 72.7, 70.1, 69.2, 66.1, 63.4, 63.0, 62.6, 58.8, 57.8, 56.9, 56.8, 49.1, 31.7, 31.3, 27.8, 25.0, 22.4, 20.0, 19.8, 11.8, 11.7, 0.2, 0.1, –3.1. HRMS (110 °C, 70 eV): *m/z* calcd for $C_{54}H_{69}O_9N_3Si_2Na$: 982.4470; found: 982.4455.

Synthesis of Tetracycle 2: Hemiaminal **15** (24 mg, 0.012 mmol) was treated with a mixture of THF (500 μL) and trifluoroacetic acid (500 μL, 0.0065 mmol) at 0 °C. The white foam of the starting material turned pink immediately after addition of the acidic solvent mixture. After stirring for 15 min the starting material had been completely consumed. Upon the removal of the trifluoroacetic acid under reduced pressure, the reaction mixture changed its color from colorless to orange and the crude product was dried under vacuum for another 30 min. The residue was dissolved in CH_2Cl_2 and the yellow solution was purified by flash column chromatography with gradient elution (hexanes–EtOAc, 9:1, then 3:1) to afford compound **2** (11 mg, 58%). R_f 0.50 (hexanes–EtOAc, 2:1); $[\alpha]_D^{20}$ –4.4 (*c* = 0.22, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.2 Hz, 2 H), 7.60 (m, 2 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 7.16–7.34 (m, 5 H), 7.07 (m, 2 H), 5.81 (m, 1 H), 5.60 (m, 1 H), 5.52 (m, 1 H), 5.07 (m, 2 H), 4.79 (m, 1 H), 4.78 (dd, *J* = 2.6, 6.9 Hz, 1 H), 4.61 (m, 1 H), 4.43 (m, 1 H), 4.24 (m, 2 H + 2 H + 1 H), 3.77 (m, 3 H), 3.71 (m, 1 H), 3.70 (s, 3 H), 3.01 (m, 1 H), 2.91 (m, 1 H), 2.54 (m, 1 H), 2.28 (s, 3 H), 2.21 (m, 3 H), 2.00 (m, 1 H), OH not found. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 150.0, 141.4, 141.3, 140.1, 136.5, 128.4, 127.9, 127.7, 127.2, 127.1, 125.3, 124.9, 122.3, 120.1, 120.0, 118.3, 116.8, 115.0, 90.4, 73.3, 70.5, 62.7, 60.9, 60.8, 54.5, 54.3, 50.8, 31.9, 20.5, 9.6. HRMS (100 °C, 70 eV): *m/z* calcd for $C_{45}H_{45}O_8N_3Na$: 778.3104; found: 778.3098.

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